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| 09/744,659 | 04/18/2001 | Michel Chevalier | 01-057 | 3396 |

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| EXAMINER |
|---|
| WINKLER, ULRIKE |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/744,659 | Applicant(s) CHEVALIER, MICHEL | |
|---|---|---|---|
| | Examiner Ulrike Winkler | Art Unit 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *11,12 and 18-21* is/are allowed.

6)☒ Claim(s) *13 and 22-31* is/are rejected.

7)☒ Claim(s) *14-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 16 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

The Amendment filed July 14, 2003 (Paper No. 15) in response to the Office Action of May 7, 2003 is acknowledged and has been entered. Claims 11-31 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

### *Claim Rejections - 35 USC § 102*

The rejection of claims 11-17, 22, 24, 25, 26, 27, 30 and 31 rejected under 35 U.S.C. 102(b) as being anticipated by Sarngadharan et al. (U.S. Pat. NO. 5,122,468) as evidenced by the product information found in the Advanced Bioscience Catalog (see Product specification Viral antigens) **is withdrawn** in view of Applicants amendments and arguments.

### *Claim Objections*

The objection of claim 23 **is withdrawn** in view of the new rejection presented below.

New rejections in view of applicant's arguments:

### *Claim Rejections - 35 USC § 102*

The rejection of claims 11-17, 22, 24, 25, 26, 27, 30 and 31 rejected under 35 U.S.C. 102(b) as being anticipated by Zaides et al. (Journal of General Virology, 1994) as evidenced by Rabenstein et al. (Biochemistry, 1995).

The instant invention is drawn to a composition comprising a trimer which has the qualities of being able to of being able to bind CD4, binding to neutralizing gp120 antibody,

binding to gp41 antibody and having no interchain disulfide bridges. Applicant has asserted that "in fact, naturally occurring trimers are known **not** to contain inter-chain disulfide linkages." The present claims do not limit the source of gp160 so this can include gp160 which is expressed from a cell line which is chronically infected with the virus. These cell lines are neither naturally occurring nor recombinant. Because as applicant asserts naturally occurring gp160 does not contain interchain disulfide bridges, the ordinary artisan would then not expect the product from a chronic virally infected cell to contain interchain disulfide bridges as well. The natural life cycle of the virus requires integration into the cell genome from which the product is then transcribed before further processing.

Zaides et al. discloses the production and purification of gp160 from a chronically infected cell line and the observation that long term culture results in the insertion of a premature stop codon deleting the transmembrane region. The resulting gp160 is secreted into the medium and is able to form oligomers, which would include trimers (see page 2967, 2nd column, last paragraph). Rabenstein et al. indicates that the leucine zipper like heptade repeat region is important for the structure formation and that gp160 forms primarily trimers and tetramers in solution (see abstract), the deleted gp160 disclosed by Zaides et al. still comprises the leucine zipper region. Therefore, the instant invention is anticipated by Zaides et al. Amending the claim to indicate that "purified recombinant trimers" are contemplated would obviate the instant rejection.

***Claim Objections***

Claims 14-17 are objected to because of the following informalities: The claims are dependent on a rejected claim, claim 13. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

Claims 22-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified recombinant trimer of HIV comprising the full length gp41 and the transmembrane form of gp41, does not reasonably provide enablement for an "comprising a gp41 fragment essential for trimer formation". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to an a purified trimer of gp160 comprising a gp41 framnet that is essential for trimer formation, neither the specification nor the art discloses the essential region in the gp41 structure that are necessary / essential for trimer formation. One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn, the limitation that only those fragments that form "trimers" are desired does not provide any guidance to the ordinary artisan to the structural limitation in the formation of the trimer that has no interchain disulfide bridges.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast

growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., Journal of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all potential fragments. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claims 22-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only pg160 purified trimers of HIV in which either the entire gp41 or the transmembrane deletion form of gp41 are present.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Furthermore, although drawn to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a

DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore only the purified trimers disclosed in the specification meets the written description provision of 35 USC 112, first paragraph.

***Conclusion***

Claims 11, 12, 18-21 are allowable.

Claims 13, 22-31 are rejected.

Claim 14-17 are objected to

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 8/8/03